Guidance for Industry

IND Meetings for Human Drugs and Biologics

Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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CMC

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

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(Due to the complexity of this draft document, please identify specific comments by line number. Use the pdf version of the document whenever possible.)

I. INTRODUCTION

This document provides guidance to industry on formal meetings between sponsors of investigational new drug applications (INDs) and the Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) on chemistry, manufacturing, and controls (CMC) information. This guidance applies to INDs for human drugs and biologics (referred to as *drugs*).[2]

This guidance covers three kinds of meetings that are held between sponsors and the Agency: (1) pre-investigational new drug application (pre-IND), (2) end-of-phase 2 (EOP2), and (3) pre-new drug application (pre-NDA) or pre-biologics license application (pre-BLA). These meetings can address questions and scientific issues that arise during the course of a clinical investigation, aid in the resolution of problems, and facilitate evaluation of drugs. The meetings often coincide with critical points in the drug development and/or regulatory process. This guidance is intended to assist in making these meetings more efficient and effective by providing information on the (1) purpose, (2) meeting request, (3) information package, (4) format, and (5) focus of the meeting when the meeting addresses CMC information.

This guidance is intended to elaborate with respect to CMC information on information in the following documents:

[1] This guidance has been prepared by the IND Reform Committee of the Chemistry, Manufacturing, and Controls Coordinating Committee (CMC CC) in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on formal IND meetings on chemistry, manufacturing, and controls information for human drugs and biologics. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

[2] The terms *investigational new drug* or *drug* as used in this guidance refer to the drug and/or biologic substance and/or product.

- Section 119 of the Food and Drug Administration Modernization Act (Pub. L. 105-115)

- Regulations applicable to meetings on investigational products in 21 CFR 312.47

- FDA guidance for industry on *Formal Meetings with Sponsors and Applicants for PDUFA Products* (draft, February 1999)[3]

- FDA guidance for industry on *Fast Track Drug Development Programs — Designation, Development and Application Review* (November 1998)

- FDA policies and procedures for formal meetings with external constituents described in CDER's Manual of Policy and Procedures (MAPP 4512.1) and CBER Standard Operating Procedures and Policies (SOPP) 8101.1

II. GENERAL ASPECTS

The general aspects of meetings provided in this guidance summarize the information provided in the formal meetings and fast track drug development guidances listed in section I and supplement this information with respect to CMC.

A. Purpose of Meeting

The purpose of meetings between sponsors and CDER or CBER on CMC information varies with the phase of the investigational study. For pre-IND meetings, the purpose is to discuss CMC issues as they relate to the safety of an investigational new drug proposed for use in initial clinical studies. The purpose of EOP2 meetings is to evaluate CMC plans and protocols to ensure that meaningful data will be generated during phase 3 studies to support a planned marketing application. Safety issues, nevertheless, will remain an important consideration during all phases of the study. The purpose of pre-NDA or pre-BLA meetings is to follow up on critical points discussed at the EOP2 meeting and to ensure that the proposed NDA or BLA will be complete and have the proper content and format to facilitate Agency review. Under certain circumstances, other types of meetings may be appropriate, such as end-of-phase 1 (EOP1) meetings for fast track drugs or meetings to discuss new protocols and/or major changes during phase 3 studies.

[3] This draft guidance is included in the list for completeness. As a draft guidance, it is not intended to be implemented until it is published as a final guidance.

B. Meeting Request

For general information on procedures for written meeting requests, sponsors should refer to the regulations, guidances, and policies and procedures listed in section I. The request should contain a list of the specific objectives and/or desired outcomes of the meeting, including a draft list of CMC-related questions.

C. Information Package

Sponsors should prepare an information package that includes a brief summary of the currently available CMC information, the developmental status, and the plan and timeline for future development of the drug. The CMC-related questions should be presented in the information package in final form, grouped together and identified. The questions should be as specific, comprehensive, and precise as possible to identify the critical issues. The questions should be presented in the same relative subject matter order as a typical CMC section of an application. Sufficient CMC background information on the drug should be provided by the sponsor in the information package to allow the Agency to address the specific questions. Sponsors should coordinate the agenda and the content of the information package to expedite review of the material and discussion at the meeting. Where data presentation is appropriate, sponsors should present a summary of the data (e.g., tables, charts, graphs).

D. Format of Meeting

1. Multidisciplinary Meeting

Usually the format of meetings prior to and during the IND stage is multidisciplinary, involving Agency personnel in clinical, pharmacology, pharmacokinetics, chemistry, microbiology, statistics, and other disciplines. Sufficient time should be allotted during multidisciplinary meetings to discuss CMC issues. The sponsor can provide a brief introductory presentation of CMC information; however, the majority of the meeting time allotted to CMC should be used to discuss specific CMC issues. Appropriate technical experts (e.g., chemists, microbiologists, biologists) representing the sponsor and the Agency should be present during all discussions of CMC-related issues.

2. CMC-Specific Meeting

Under appropriate circumstances, a separate CMC-specific meeting may be held in addition to, or as an alternative to, the multidisciplinary format. For example, a CMC-specific meeting is encouraged to discuss CMC issues that are too extensive or detailed to be adequately addressed in a multidisciplinary meeting, or are otherwise beyond the scope of a multidisciplinary meeting.

E. Focus of Meeting

Meetings should focus primarily on addressing the specific questions listed in the information package. The Agency may also wish to discuss relevant questions on safety issues or various scientific and/or regulatory aspects of the drug (see sections III, IV and V). These can arise from Agency guidance documents, the reviewing division's experience, the manufacturing industry's experience, or scientific literature. The actual questions, issues, and/or problems discussed at a given meeting will be specific to the sponsor, drug, route of synthesis or isolation, dosage form, formulation, stability, route of administration, dosing frequency, or duration.

The following sections provide specific guidance and more detailed information on each of the three basic types of meetings, pre-IND, EOP2 and pre-NDA or pre-BLA, as well as examples of the CMC issues typically addressed in each of these meetings.

III. PRE-IND MEETING

A. Purpose of Meeting

With respect to CMC information, the purpose of pre-IND meetings for phase 1/phase 2 is to discuss safety issues related to the proper identification, strength, quality, purity, or potency of the investigational drug, as well as to identify potential clinical hold issues.[4]

B. Meeting Request, Information Package, and Format

See section II above for general aspects regarding the meeting request, information package, and format for the meeting.

C. Focus of Meeting

The pre-IND meeting should focus on the specific questions related to the planned clinical trials. The meeting can also include a discussion of various scientific and regulatory aspects of the drug as they relate to safety and/or potential clinical hold issues. Examples of the CMC issues that could be discussed in pre-IND meetings include, but are not limited to:

- Physical, chemical, and/or biological characteristics

[4] See FDA guidance for industry on *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biology-Derived Products* (November 1995).

- Manufacturers
- Source and method of preparation
- Removal of toxic reagents
- Quality controls (e.g., identity, assay, purity, impurities profile)
- Formulation
- Sterility (e.g., sterilization process, release sterility and endotoxin testing, if applicable)
- Linkage of pharmacological and/or toxicity batches to clinical trial batches
- Stability information

The discussion of safety issues for conventional synthetic drugs is typically brief. For certain types of drugs, such as biotechnological drugs, biological drugs, complex dosage forms, and drug-device combinations, it may be appropriate to discuss the CMC information in more detail. Examples where detailed discussion may be appropriate include, but are not limited to:

- Drugs from human sources (e.g., appropriate donor screening procedures for tissues, blood, or other fluids; removal or inactivation of adventitious agents (e.g., viruses, bacteria, fungi, mycoplasma)
- Drugs from animal sources (e.g., removal or inactivation of adventitious agents, transmissible spongiform encephalopathy (TSE)-free certification)
- Biotechnology drugs, particularly rDNA proteins from cell line sources (e.g., adequacy of characterization of cell banks, potential contamination of cell lines, removal or inactivation of adventitious agents, potential antigenicity of the product)
- Botanical drugs (e.g., raw material source, absence of adulteration)
- Reagents from animal or cell line sources (same considerations as for drugs derived from animal cell or cell line sources)
- Novel excipients
- Novel dosage forms (e.g., characteristics, potential for overly rapid release of dose, if applicable)

- **!** Drug-device delivery systems (e.g., demonstration of device and its characteristics, potential for overly rapid release of dose, particle size distribution considerations, where applicable)

IV. END-OF-PHASE 2 MEETING

A. Purpose of Meeting

The purpose of the EOP2 meeting, with respect to CMC information, is to provide an opportunity for the sponsor and reviewing division to (1) evaluate the results of the drug development program to date; (2) discuss the sponsor's plans and protocols relative to regulations, guidances, and Agency policy; (3) identify safety issues, scientific issues, and/or potential problems and resolve these, if possible, prior to initiation of phase 3 studies; and (4) identify additional information necessary to support a marketing application. The CMC portion of the EOP2 meeting is a critical interaction between the sponsor and the chemistry review team to ensure that meaningful data will be generated during phase 3 studies. The goal is to identify potential impediments to further progress at an early stage, thus reducing the number of review cycles for the proposed marketing application. Although the EOP2 meeting is important for all drugs, it is particularly important for new molecular entities, biotechnology drugs, complex dosage forms, and/or drug-device delivery systems.

B. Meeting Request, Information Package, and Format

See section II for general aspects of the meeting request, information package, and format for the meeting. A multidisciplinary or separate CMC-specific EOP2 meeting may be held. If a CMC-specific meeting is held, it is preferred that it be scheduled to take place immediately prior to or after the meeting on clinical issues. Under appropriate circumstances, such CMC-specific meetings may occur during phase 3 trials, but prior to phase 3-associated scale-up and manufacturing changes.

C. Focus of Meeting

The EOP2 meeting will focus on the CMC-specific questions on the planned phase 3 studies. Typically the meeting will also include a discussion identifying additional information to support a marketing application. Examples of the CMC issues that may be addressed in EOP2 meetings include, but are not limited to:

1. All Drugs

- Unique physicochemical (e.g., polymorphic forms, enantiomers) and biological properties
- Adequacy of physicochemical characterization studies
- Starting material designation
- Coordination of all activities, including full cooperation of any contractors and suppliers in support of the planned NDA or BLA
- Qualification of impurities (update from phase 1)
- Removal or inactivation of adventitious agents (update from phase 1, where applicable)
- Approach to specifications (i.e., tests, analytical procedures, and acceptance criteria)
- Coordination between sponsor and Agency chemists and pharmacokineticists to establish proper dissolution test procedures (particularly because dissolution testing will be included in the stability protocols, where applicable)
- Link between formulations and dosage forms used in preclinical, clinical, pharmacokinetic/pharmacodynamic studies, and formulations planned for the NDA or BLA
- Specific considerations for container/closure system components for specialized delivery systems such as metered dose inhalers (MDIs), dry powder inhalers (DPIs), disposable pen injectors, transdermal patches, or other novel dosage forms
- Approach to sterilization process validation and/or container closure challenge testing, where applicable
- Devices (e.g., pumps, valves, cartridge injectors, actuators), where applicable
- Appropriateness of the stability protocols to support phase 3 studies and the planned NDA or BLA

- Major CMC changes, including site changes, anticipated from phase 2 through the proposed NDA or BLA, ramifications of such changes, and appropriateness of planned comparability and/or bridging studies, if applicable

- Environmental impact considerations, if pertinent

- Identification of any other CMC issues, including manufacturing site, which pose novel policy issues or concerns, or any other questions, issues or problems that should be brought to the attention of the Agency or sponsor

2. rDNA Protein Biotechnology Drugs

In addition to the items listed in section IV.C.1, CMC issues that may be addressed in EOP2 meetings for rDNA protein biotechnology drugs include, but are not limited to:

- Adequacy of physicochemical and biological characterization (e.g., peptide map, amino acid sequence, disulfide linkages, higher order structure, glycosylation sites and structures, other post-translational modifications, and plans for completion, if still incomplete)

- Bioassay (e.g., appropriateness of method, specificity, precision)

- Adequacy of cell bank characterization (e.g., update from phase 1, plans for completion, if still incomplete)

- Removal of product- and process-related impurities (e.g., misfolded proteins, aggregates, host cell proteins, nucleic acid)

- Bioactivity of product-related substances and product-related impurities relative to desired product

3. Conventional Biologics

In addition to the items listed in section IV.C.1-2, CMC issues that could be addressed in EOP2 meetings for conventional biologics (e.g., nonrecombinant vaccines and blood products) include, but are not limited to:

- Coordination of facility design

- Process validation considerations

- Potency assay

V. PRE-NDA OR PRE-BLA MEETING

A. Purpose of Meeting

The purpose of the pre-NDA or pre-BLA meeting is to (1) discuss the drug development program to date, (2) exchange information about the proposed marketing application, (3) identify and resolve, if possible, potential refuse-to-file issues, (4) facilitate review of the proposed marketing application, and (5) identify any major unresolved problems that might remain. The CMC portion of the pre-NDA or pre-BLA meeting is a critical interaction between the CMC review team and the sponsor to ensure the submission of a well-organized and complete NDA or BLA.

B. Meeting Request, Information Package, and Format

See section II for general guidance on the meeting request, information package, and format for the meeting. A pre-NDA or pre-BLA meeting should be held about 6 months prior to the planned NDA or BLA submission date, or earlier if new CMC issues and/or major changes in information discussed in the EOP2 meeting will be presented.

C. Focus of Meeting

The pre-NDA or pre-BLA meeting should focus on addressing the specific questions related to filing and format issues. Typically the meeting also includes a discussion to identify problems that may cause a refuse-to-file recommendation or hinder the review process. Examples of CMC issues that could be addressed in pre-NDA or pre-BLA meetings include, but are not limited to:

- Confirmation that all outstanding issues discussed at the EOP2 meeting or raised subsequently will be adequately addressed in the proposed NDA or BLA

- Coordination of all activities, including full and timely cooperation of any contractors and suppliers, in support of the proposed NDA or BLA

- Discussion of the relationship between the manufacturing, formulation, and packaging of the drug product used in the phase 3 studies and the final drug product intended for marketing, and assurance that any comparability or bridging studies have been appropriately completed

- Assurance that the submission will contain adequate stability data in accordance with the agreed upon stability protocols

- Confirmation that all facilities (e.g., manufacturing, testing, packaging) will be ready for inspection by the time of the NDA or BLA submission

- Discussion of the format of the proposed NDA or BLA submission, including whether an electronic submission will be provided

- Identification of any other issues, potential problems, or regulatory issues that should be brought to the attention of the Agency or sponsor

REFERENCES

FDA guidance for industry on *Content and Format of Phase I Investigational New Drug Applications (INDs) for Phase I Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (November 1995).

FDA, *CDER Manual of Policies and Procedures (MAPP) 4512.1, Training and Communications, Formal Meetings between CDER and External Constituents*, March 1996 (http://www.fda.gov/cder).

FDA, *Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants*, CBER Standard Operating Procedures and Policies (SOPP) 8101.1 (http://www.fda.gov/cber).

FDA, guidance for industry on *Formal Meetings with Sponsors and Applicants for PDUFA Products* (Draft, February 1999).

FDA guidance for industry on *Fast Track Drug Development Programs — Designation, Development and Application Review* (November 1998).

FDA guidance for industry on *CMC Content and Format of Investigational New Drug Applications (INDs) for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic Biotechnology-Derived Products* (Draft, February 1999).